REMARKS

This application is a 371 filing of PCT International application PCT/EP2005/001037 filed February 2, 2005 and amended under PCT Article 19 on May 23, 2005. Original claims 1-12 are cancelled above; new claims 13-20 correspond to the Article 19 amended claims and are presently pending. No new matter has been added.

REJECTION OF CLAIM 1 UNDER 35 U.S.C. § 101

The Examiner also rejects claim 1 under 35 U.S.C. §101, alleging the claim recites a use, without setting forth any steps involved in the process. Applicants respectfully disagree. New claim 13 recites a method for the early determination of the risk of mortality of patients in intensive care units for whom the clinical diagnosis is sepsis, severe sepsis or septic shock, comprising: obtaining a serum or plasma sample of a patient in intensive care units for whom the clinical diagnosis is sepsis, severe sepsis or septic shock, and selectively determining the concentration of Cu/Zn SOD in said sample by means of an immunochemical assay method specific for Cu/Zn superoxide dismutase (Cu/Zn SOD or SOD-1), wherein concentrations of Cu/Zn superoxide dismutase which are above a predetermined cut-off are correlated with a high risk of mortality. As such, claim 13 does not recite a use without setting forth steps involved in the process, as alleged by the Examiner. Therefore, Applicants respectfully request withdrawal of this rejection in view of new claim 13.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

In item 7 and 8 of the Office Action, the Examiner rejects claim 1 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner alleges that there are no positive active method steps for performing the method. In response, Applicants respectfully point out that new claim 13 includes the method steps of obtaining…, and determining…, which are active tense verbs. New claim 13 also concludes with a step relating the method result to the purpose of the method. Thus, Applicants respectfully request withdrawal of

this rejection in view of new claim 13.

The Examiner alleges that recitation of "early" in claim 1 renders the claim as indefinite under 35 U.S.C. §112, second paragraph. In response, Applicants contend that early diagnosis or early determination of risk would have a clear meaning to a person of ordinary skill in the art. In particular, Applicants point to support found for example in paragraphs [0009], [0023], [0026], and [0027] of the application as filed. For example, the application discloses "early stage of a sepsis…early diagnosis of a sepsis…and early distinction between a sepsis due to infection and severe inflammations…" The application further points out that there is an urgent need for additional biomarkers for precise sepsis diagnosis and in particular for early sepsis diagnosis. Moreover, the application teaches that their invention relates to the observed course of the disease or course of the sepsis and in particular permits a reliable early assignment of critically ill patients to the groups consisting of the patients who will probably survive and to the patients who will not survive. Thus, in view of the teachings of the present invention, Applicants respectfully contend that the term "early" would have a clear meaning to a person of ordinary skill in the art and therefore respectfully request withdrawal of this rejection.

Claim 4 is rejected under 35 U.S.C. §112, second paragraph as being vague for reciting "310 ng/ml or more." Applicants respectfully point out that this concentration was determined by Applicants as a preferred cut-off for the prognosis "100% mortality risk" or "high probability of survival" and therefore 310 ng/ml or more is clear and particularly points out and distinctly claims the subject matter which Applicants regard as their invention. Thus, Applicants respectfully request withdrawal of this rejection.

Claim 5 is rejected under 35 U.S.C. §112, second paragraph for recitation of "parameter" in the claim. New claim 17 which corresponds to former claim 5 indicates that the method includes the measurement of the concentration of at least one additional "marker"; it is clear from new claim 18, which follows, that the marker is a protein biomarker.

Claim 6 is rejected under 35 U.S.C. §112, second paragraph for including the term "in particular" in the claim. In response, Applicants point out that new claim 18 excludes the term "in particular." The Examiner objected to claim 6 because of the use of an acronym, e.g. TPS and

CHP. In response, new claim 18 defines acronyms, including TPS and CHP.

Further, the Examiner alleges that claim 6 lacks sufficient antecedent basis for "the peptide inflammin," "the peptide hormones," and "the C-reactive protein." New claim 18 has sufficient antecedent basis and as such, Applicants respectfully request that this rejection be withdrawn.

Claim 8 has been cancelled and no corresponding claim currently is pending.

Claim 9 is rejected under 35 U.S.C. §112, second paragraph for including the phrase "(accelerated test)" in the claim. In response, Applicants point out that new claim 21 excludes this term in its entirety. As such, Applicants respectfully request that this rejection be withdrawn.

In view of the above amendments, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a)

Claims 1-3 and 5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Warner *et al.* (Clin Chemistry 41/6, p. 867-871, 1995; hereinafter "Warner.") and Galikowski *et al.* (Research in Surgery, vol. 6, no. 1, 1994; hereinafter "Galikowski"), in view of Uda *et al.* (EP 021175542; hereinafter "Uda")[2]. In particular, the Examiner alleges that Warner discloses determining enzyme concentrations of superoxide dismutase (SOD) in plasma samples of septic patients, and that Galikowski teaches that the increased enzymatic activity of Warner would include increase activity of SOD-1. The Examiner further alleges that Uda teaches that SOD-1 concentrations can be determined in patient samples with extremely high specificity and, therefore, the Examiner alleges that Uda can be used in diagnostic methods as taught by Warner and Galikowski. Applicants respectfully disagree that new claim 13 is obvious over Warner and Galikowski, in view of Uda for the following reasons.

WARNER

As the Examiner correctly states on pages 8-9 of the Office Action, Warner does not disclose a selective determination of Cu/Zn SOD (SOD-1) concentrations. In Warner, a general

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2 Warner, Galikowski and Ude references cited by the Examiner were also considered by the European Patent Office

SOD activity (total plasma SOD) is determined by an assay which does not distinguish between the three known isoforms of SODs (*see* Warner, page 868, right column, lines 4-5: "The method does not differentiate between the three isoforms of SOD.").

It is, however, well known that *e.g.* SOD-1 and SOD-2 are expressed differently in a number of diseases (*see* for example, Götz *et al.* and Kruidenier *et al.*, previously disclosed in an IDS). Götz, in the Abstract, under "Results", states that in Helicobacter pylori infection Mn SOD (SOD-2) increased by about 2-fold to 3-fold whereas Cn/Zn SOD (SOD-1) showed a slight decrease in gastric mucosa (*see* also "Conclusion"). Kruidenier, in the Abstract, lines 12 to 19, reports similar results for inflammatory bowel disease (increase of Mn SOD protein levels in mucosa specimens, Cu/Zn SOD decrease with infection). Although Götz and Kruidenier investigated mucosa tissue of different origin, whereas the present invention concerns a selective determination of SOD-1 in blood based samples (serum, plasma), Götz and Kruidenier clearly show that SOD-1 and SOD-2 are expressed differently.

As is discussed in the present specification (*see* paragraph numbers [0020] and [0023]), most prior art references deal with SOD in general and include a co-determination of Mn SOD (SOD-2; a mitochondrial enzyme of about 80 kDa) the physiological occurrence of which is clearly distinct from SOD-1 and/or use enzymatic methods for the determination of SOD activity. If only the total enzymatic SOD activity (total SOD) is determined, an increase in Mn SOD (SOD-2) may be upset be a decrease of Cu/Zn SOD (SOD-1), and no clear results may be obtained.

The Examiner alleges that Warner discloses determining enzyme concentrations of superoxide dismutase (SOD) and comparing the concentrations to a predetermined cut-off and determining increases for prognosis. However, Applicants point out that Warner (*see* first paragraph) found very high SOD activity in 7 of 21 (30%) of the non-survivors, and, therefore, concluded that "high total plasma SOD activity appears to have some potential as a prognostic indicator". Yet, a majority, namely 70%, of the non-survivors did **not** have such high total plasma SOD activity.

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and are cited and discussed in the granted EP patent.

These results of Warner are to be compared with the results of the selective immunodiagnostic measurement of SOD-1 according to the present invention, where significant concentration changes (increases) where found for **all** non-survivors. Warner, therefore, rather represents the prior art according to Figure 2 and does not anticipate or make obvious the claimed invention.

It was by no means obvious that by (i) selectively measuring only one SOD isoform (SOD-1) (ii) using of a properly calibrated immunodiagnostic method the prognostic validity of a determination in sepsis patients can be highly improved.

GALIKOWSKI

While admitting that Warner fails to teach determining the concentration of SOD-1 in a sample, the Examiner alleges that Galikowski teaches that SOD-1 activity is increased during sepsis. Applicants respectfully contend that Galikowski does not add anything to the teachings of Warner. Galikowski describes an investigation of an antibiotic prophylaxis with cefoperazone using a rabbit model. Among the determined parameters is a so-called SOD-1 activity. Said "SOD-1 activity," however, is determined by an enzymatic method of adrenaline autoxidation (page 32, right column) described in previously cited IDS reference Misra *et al.*, The Journal of Biological Chemistry, Vol. 217, pp. 3170-3175, 1972. The proposed "Assays for Superoxide Dismutase" are described on page 3174, right column. Superoxide dismutase (SOD), which may be a constituent of a biological sample to be investigated, can be assayed in terms of its ability to inhibit epinephrin (adrenaline) autoxidation, under specific conditions. The underlying effect of superoxide dismutase is that it acts as potent inhibitor of the autoxidation due to its ability to catalyze the formation of hydrogen peroxide from superoxide anions O_2^- (*see* Warner, page 867, right column, lines 7-8) and thereby removes O_2^- from the reaction system. This effect, however, is not specific for SOD-1, and the mention of "SOD-1" in Galikowski in fact does not seem correct, because the assay of Misra *et al.* is not specific for SOD-1 but rather is a total SOD assay.

Moreover, in Galikowski, no relation whatsoever is made between the measured SOD activity and the mortality of sepsis patients. There is no information whatsoever whether some,

part of or all rabbits died, and whether the measured SOD activities were related to the mortality of the rabbits. Further, in Galikowski SOD-1 is discussed as protective factor, not as prognostic factor for an increased mortality risk.

UDA

Uda discloses an immunoassay for the specific determination of Cu/Zn SOD (SOD-1) in serum for diagnosing and testing a human cancer of the stomach, *i.e.* they provide a tool for diagnosing stomach cancer. The present inventors, who used a commercially available assay themselves (see [0044]), do not claim a new assay, but a prognostic method concerning the mortality risk of sepsis patients. No disclosure linking SOD-1 concentrations in the blood of sepsis patients with their mortality risk can be found in Uda.

WARNER AND GALIKOWSKI IN VIEW OF UDA

It would not have been obvious to one of ordinary skill in the art to combine Warner and Galikowski in view of Uda and arrive at the present invention. As is discussed in detail *supra*, Warner discloses determining general SOD activity (total plasma SOD) by an assay which does not distinguish between the three known isoforms of SODs (*see* Warner, page 868, right column, lines 4-5). Galikowski does not remedy the deficiencies of Warner, and Uda fails to even disclose linking SOD-1 concentrations in the blood of sepsis patients with their mortality risk. As such, there is no teaching, suggestion or motivation to combine Warner and Galikowski in view of Uda to arrive at the present invention.

The present invention is based on the finding that immunodiagnostically measured values of the concentration of a certain protein (SOD-1) in a serum or plasma sample of a patient (sepsis patient) constitute a new and highly relevant predictive (prognostic) biomarker for the chance of survival (or mortality risk) of sepsis patients with high validity (see for e.g. paragraph [0026]). The defined chemical entity, namely the enzyme (protein) Cu/Zn superoxide dismutase ("Cu/Zn SOD"; alternative abbreviation: "SOD-1"; a cytosolic enzyme of about 33 kDa) is determined by a method which measures only said protein (*i.e.* by an immunodiagnostic method which is selective for said protein) and can be calibrated for the measurement of its concentrations.

There exist different SODs which are different chemical entities (proteins with different sequences of amino acids). Determination methods relying on the detection/measurement of an enzymatic action (enzymatic assays) do not distinguish between different SODs but give only a summary result in terms of a total enzyme activity. Enzymatic activity, is influenced by other factors than just the concentration of the enzyme. Said other factors, which can *e.g.* be measuring conditions, presence of inhibitors/activators in the sample or the like, may enhance or decrease a measured enzymatic activity which, therefore, is not the same as the concentration or amount of a molecule measured by an immunoassay.

In contrast to the results of a selective immunodiagnostic measurement of "SOD-1" concentrations, the results of measurements of the enzymatic activity (SOD activity) are not useful for the prognostic purposes of the invention (mortality risk). This clearly is shown in Figure 2 (enzyme assay) which is to be compared with Figure 1 (immunodiagnostic assay) and Figure 3.

Therefore, at least for this additional reason, no combination of Warner, Galikowski or Uda teach or suggest the present invention. As such, Applicants respectfully request that rejection of claims 1-3 and 5 under 35 U.S.C. § 103(a) be withdrawn.

The Examiner further rejects dependent claims 4, 6, and 7-9 under 35 U.S.C. § 103(a) based on the same combination of three references as discussed *supra,* further in view of additional references. Applicants respectfully point out that claim 1 is non-obvious over Warner and Galikowski in view of Uda for the reasons adumbrated *supra*, and that the rejection of dependent claims 4, 6, 7-9, requiring additional references, is moot in view of the above.

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

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